EXHIBIT A

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

JULY 7, 2011

Access to Safety Data — Stockholders versus Prescribers

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The legal and medical systems both strive for truth while acknowledging that there are no absolutes. Both systems require evidence, which they categorize in a hierarchy of levels, on which to base decisions that can have major effects on the quality and even quantity of people's lives. In law, the strictest standard of proof applies in criminal matters, in which the presumption of innocence requires that guilt be established "beyond a reasonable doubt" to attempt to rule out the possibility of convicting an innocent person — though of course the application of this level of proof carries the risk of occasional acquittal of a defendant who is actually guilty. A lower, but still relatively stringent, standard of proof, that of "clear and convincing" evidence, applies to certain discrete civil matters and criminal matters such as the setting of bail. A still lower standard requiring conclusions based on a "fair preponderance of the evidence" applies in the great majority of civil matters, and an even lower standard in which only "probable cause" must be established permits certain criminal proceedings to be initiated.

These levels of legal proof have analogies in medicine. Clinical trials use alpha (significance) levels, confidence intervals, and statistical power to gauge levels of certainty. To reject the null hypothesis (that a result occurred merely by chance) and deem an intervention effective in a clinical trial, the level of proof analogous to law's "beyond a reasonable doubt" standard would require an extremely stringent alpha level to permit researchers to claim a statistically significant effect, with the offsetting risk that a truly effective intervention would sometimes be deemed ineffective. Instead, most randomized clinical trials are designed to achieve a somewhat lower level of evidence that in legal jargon might be called "clear and convincing," making conclusions drawn from it highly probable or reasonably certain.

Although errors can be made by both the judicial system and the medical research system, the former provides the opportunity to appeal a court's decision, and in the latter, reproducibility or independent confirmation of a result greatly enhances the reliability of findings. Unlike the categorical decisions of the courts, which immediately carry the weight of

the law regardless of their popularity,[1] the results of a clinical trial can have greater or lesser impact depending on their eventual degree of acceptance by the medical community. The data from clinical trials are generally initially disseminated in peer-reviewed medical journals, at scientific meetings, or both. The ultimate influence of a study then depends on the interpretation of the importance of its results by national guideline-setting committees, as well as by more local physician groups at journal clubs, morning reports, and rounds. In such scholarly dissections of the trial data, statistical tests represent only one aspect of the intense scrutiny applied in assessing the quality and robustness of the findings.

In the recent unanimous decision in *Matrixx Initiatives v. Siracusano*, the U.S. Supreme Court applied the "fair preponderance of the evidence" standard of proof used for civil matters, in which a particular conclusion is deemed "more likely than not" to be justified.[2] At issue was whether Matrixx had violated federal securities laws by failing to disclose to shareholders sporadic reports of anosmia associated with the use of its Zicam nasal spray before the Food and Drug Administration (FDA) issued a warning about that association in 2009. The question before the Court was not whether the drug caused the loss of smell, but rather whether the company failed to provide material information to the investor plaintiffs that would have led a "reasonable shareholder" to alter his or her investment strategy. The initial trial court was persuaded by the company's primary argument that the evidence suggesting that its product caused anosmia did not reach statistical significance and therefore should not have been considered material. In upholding the ruling of the appellate court, which had reversed the trial court's decision, the Supreme Court ruled that whether or not it was considered statistically significant, the information about the seemingly infrequent occurrences of loss of smell after use of the product was indeed material to investors. Speaking for the undivided Court, Justice Sonia Sotomayor also acknowledged that the mere existence of reports of adverse events associated with a drug does not prove causality — but asserted that such a high level of proof did not have to be achieved.[2] Similarly, under the Code of Federal Regulations for the FDA, warnings and precautions regarding the safety of drugs must be revised to include information on "a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established."[3] There is no requirement for statistical significance.

Clinicians are well aware that to be considered material, information regarding drug safety does not have to reach the same level of certainty that we demand for demonstrating efficacy. We understand that clinical trials that are designed to prove that a drug is effective use preplanned statistical analyses focused on a specific, carefully defined and adjudicated primary end point. Moreover, the number of subjects who will have to experience this targeted event for researchers to adequately test whether it occurs at the same rate as it does in a comparison group (the trial's statistical power) is also established before the study begins. This same carefully constructed statistical framework is not, and understandably cannot be, used for evaluating unplanned and uncommon adverse events. When studying safety, we search for signals of imbalances and attempt to piece together multiple underpowered comparisons to obtain a better estimate of the risk.

Sorting the wheat of true adverse drug effects from the chaff of biologic variability and chance associations is exceedingly difficult. A staggering and increasing number of reports are received by the FDA's Adverse Event Reporting System (AERS) each year — more than half a million in 2009. National efforts are under way to link together large administrative databases to permit hypotheses concerning adverse associations to be tested more rigorously.[4] To enable medical sleuths to detect the initial scent that leads them to track a low-frequency adverse drug effect, more open and better reporting is needed. But fuller reporting of all adverse experiences without filtering on the basis of statistical significance or perceived causality would result in the publication of more tedious supplemental tables that primarily contribute to information overload. Similarly, Justice Sotomayor noted that such unfiltered information "could bury the shareholder in an avalanche of trivial information."[2] However, in cases in which data showing initially seemingly unimportant imbalances eventually add up to a clear signal of an adverse action of a drug, transparent early reports could re-

duce the likelihood of litigious arguments concerning who knew what and when.[5] Individual manufacturers should not be in the position of determining what information is considered material for public dissemination.

Physicians are also well aware that our noninfallible but important recommendations are based on our best assessments of incomplete data, with levels of evidence ranging from firm to anecdotal. With the finality afforded by the Supreme Court decision in *Matrixx*, investors can be assured of increased access to statistically nonsignificant information regarding reports of adverse drug experiences. Although the medical establishment lacks legal authority, it could use its standards-setting powers to improve access to the same level of information. The resulting flood of data, though likely to represent biologic noise rather than evidence sufficient to establish even "probable cause," would contribute to the total mix of available information and might, under some circumstances, influence reasonable prescribers and patients to alter their treatment plans: a sommelier, for example, might consider any report of anosmia to be material.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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This article (10.1056/NEJMp1104699) was published on June 29, 2011, at NEJM.org.

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New FDA Regulation to Improve Safety Reporting in Clinical Trials

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As part of an initiative designed to modernize the clinical trial enterprise, the Food and Drug Administration (FDA) recently published a regulation establishing a new safety-reporting paradigm for drugs being studied under investigational new drug applications (INDs).[1] This rule — published last September and effective as of March 28, 2011 — is one in a series of steps the FDA is taking to enhance the protection of human subjects and improve trial conduct by streamlining the regulatory procedures for clinical trials.

Monitoring patient safety during clinical trials is a critical component of the drug-development process. Such monitoring is a dynamic process intended to protect trial volunteers from preventable harm. It depends on observant investigators, responsible analysis by trial sponsors, and prompt reporting to the FDA, all investigators, and institutional review boards (IRBs) of serious new adverse reactions. Although safety databases are scrutinized when applications for marketing approval are submitted, ongoing safety analyses during trials are critical in ensuring that serious adverse events are discovered as soon as possible. Safety data from ongoing clinical trials influence the clinical care of patients enrolled in those and other trials of a given drug; if the drug is already on the market, these data may affect its clinical use. Safety reports derived from ongoing clinical trials must be meaningful, relevant, and amenable to timely analysis.

The new regulation clarifies the responsibilities of clinical investigators and IND sponsors with respect to the reporting and analysis of serious, unexpected events that are suspected to be caused by the drug. Because the FDA's previous safety-reporting requirements were not specific regarding the threshold for deeming an adverse event reportable, IND sponsors were often reporting to the agency and clinical investigators, in an expedited manner (typically within 15 days), substantial numbers of serious adverse events, without enough context to permit evalu-